GloboMax LLC

GloboMax Responses to A. Retzios's Comments for Phase III Emitasol Protocol-

Comment #1 Synopsis Secondary Objective #2

Having read the protocol, it is very unclear how the pharmacokinetic – pharmacodynamic relationship is going to be defined. The pharmacokinetic section (which I think should be dropped) of this study and the planned meta-analysis do not offer any suggestions as to how the pharmacokinetic data will be used to derive pharmacodynamic information and the nature of the pharmacodynamic information sought. Are we planning specific pharmacodymanic tests such as lower esophageal sphincter pressure measurements or something like it? The gastric emptying test seems to fit the bill, but what will be its use vis-à-vis the pharmacokinetics if it is going to be performed only to a subset of patients?

- *Response: To address the question, we will include a plan for the PK and PK/PD analysis as an Appendix to the protocol. The pharmacokinetic section can not be dropped. The pharmacokinetics of this drug is variable and not well defined. This intersubject variability is of a special FDA concern, as discussed at the FDA meeting. The PK/PD study does not have enough patients (80 on the nasal spray) to define the relationships between the pharmacokinetic parameters and the covariates. A PK analysis from the phase III study will allow an estimation of the individual patient exposure (AUC) from 3 samples drawn from a patient (one sample at Visits 2,3, and 4). The pharmacokinetic –pharmacodynamic analysis will seek relationships between:*
    1. *Change from baseline for total symptom score as a function of systemic exposure, treatment duration and covariates,*
    2. *Probability to prematurely withdraw from the study versus efficacy, duration of treatment and covariates.*

- *Recommend that we add the following information:*

APPENDIX VIII. PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetic analysis

Plasma concentration data collected in this trial will be combined with the data from the pivotal pharmacokinetic - pharmacodynamic study for population pharmacokinetic analysis.

Objectives

The objectives of the analysis will be to:

1. Estimate pharmacokinetic parameters of the nasal spray in the target patient population;
2. Estimate variability of the pharmacokinetic parameters;

3. Determine the influence of possible covariates (demographic, drug interactions, etc) on pharmacokinetic parameters.

Analysis populations

All patients from the active treatment arms with at least one plasma concentration measurement, documented time of the measurement and time of the preceding dose will be included in the analysis. Patients from the placebo group will not be included in the pharmacokinetic analysis.

Sample size considerations

There is no formal power calculation for a population pharmacokinetic modeling analysis. Sample size, as well as the number of samples per individual, are factors that influence the accuracy and precision of model parameter estimates and the ability to define a suitable model. In this regard, combined data from the pivotal pharmacokinetic - pharmacodynamic study and this study will serve the purpose of defining a population pharmacokinetic model. This conclusion is based on past experience with mixed effects pharmacokinetic modeling and prior knowledge of metoclopramide pharmacokinetics. With the current protocol and expected data, fixed effects PK parameters should be estimated with precision and accuracy, while random effects parameters (inter- and intra-individual variability) could be less precise.

Covariates

Covariates available for assessment will include patient demographics, clinical laboratory values, medical history, and frequently used concomitant medications. Demographics will include sex, age, weight, race, obesity measure, body surface area, smoking, and alcohol consumption. Clinical laboratory values will include baseline values for creatinine clearance, liver function tests, albumin and total protein. Medical history will include cardiovascular disease, type and duration of diabetes, and a baseline value for total symptom score. Concomitant medications will include drugs used by 40 or more patients (around 10 % of patients on metoclopramide nasal spray). The effects of these covariates on the pharmacokinetic parameters will be investigated.

Missing covariates

Missing covariates will be replaced with the population median value for that covariate. If a significant number (> 15%) of any covariate value is missing, that covariate will not be used in the analysis.

Model development

The population pharmacokinetics will be analyzed by mixed-effects modeling using NONMEM. First, the structural (compartmental) and statistical (variability) models will be established (without the inclusion of covariates). The pharmacokinetic data will initially be fit to a one- and two- compartment linear model as the base structural model. More complex models will be fit to the data if warranted by diagnostic plots. Individual parameter estimates will be obtained. Next, an exploratory analysis (Generalized Additive Modeling and exploratory graphics) will be conducted on the relationship between pharmacokinetic parameters and demographic covariate factors. The influential

covariates will be explicitly incorporated into the population pharmacokinetic model by making the typical values of the structural pharmacokinetic parameters a function of the covariate. NONMEM regression analysis will be performed on the model with covariate parameters being added in the model building process and subtracted in the model reduction process. The Likelihood Ratio Test will be used to evaluate the significance of incorporating parameters into the population model. Any fixed effect that reduces the minimum objective function (MOF) by more than 3.84 (χ^2, $p<0.05$;df=1) will be considered significant and added to the model. After all statistically significant covariates are added to the model, their importance will be evaluated again by eliminating each covariate from the model, one at a time. The covariate will be excluded if the MOF does not increase by more than 6.6 (χ^2, $p<0.01$;df=1) and no substantial increase occurs in the corresponding random effect parameter.

Model validation
The predictive performance of the model will be assessed. Plots of random effects (residuals and inter-individual errors) of validation data sets versus covariates will provide information on the clinical significance of covariates.

Pharmacodynamic analysis

Objectives

1. To assess the relationship between efficacy (as measured by change from baseline of the total symptom score) versus systemic exposure, duration of treatment and covariates.

2. To assess the relationship between the probability to prematurely withdraw from the study versus efficacy, duration of treatment and covariates.

Analysis populations
All patients from the active treatment groups with at least one post-baseline efficacy assessment and at least one plasma concentration measurement with documented time of the measurement and time of the preceding dose will be included in the analysis. Patients from the placebo group with at least one post-baseline efficacy assessment will also be included.

Response variables
Change from baseline in the total symptom score and probability to withdraw from the study will be the response variables of two separate models.

Covariates
The individual patient exposure (AUC) will be estimated using the population pharmacokinetic model developed in the pharmacokinetic analysis. Individual exposures will be used as covariates in the development of pharmacokinetic-pharmacodynamic models. The other covariates will be the same as in the pharmacokinetic analysis.

Model building
Mixed-effects population models will be built using NONMEM. The modeling process will follow the same procedures as model building for the population pharmacokinetic model. Models for the placebo effect will be determined based on the response of patients in the placebo group and will be incorporated as part of the pharmacodynamic effect. Structural models for placebo and drug effects and for dropouts will first be investigated by exploratory techniques. Candidate models will then be incorporated into NONMEM.

Validation
Change from baseline in total symptom score conditional on the drop out times will be simulated based on the models for drop out and unconditional model for change in total symptom score. Simulated responses will be compared with the observed data.

- *Change in Synopsis (Pharmacokinetics/Pharmacodynamics):*

From: Individual patient exposures will be estimated from pharmacokinetic analysis. Pharmacokinetic-pharmacodynamic analysis will correlate efficacy as assessed by changes in symptomology with estimated individual exposure, demographic covariates, and duration of treatment.

To: Individual patient exposures will be estimated from pharmacokinetic analysis. The objectives of pharmacokinetic-pharmacodynamic analysis will be:

1. To assess the relationship between efficacy (as measured by change from baseline of the total symptom score) versus systemic exposure, duration of treatment and covariates.
2. To assess the relationship between the probability to prematurely withdraw from the study versus efficacy, duration of treatment and covariates.

- *Change in Section 11 (Pharmacokinetics/Pharmacodynamics):*

From: The PK/PD relationship will be investigated, to assess the relationship between efficacy, systemic exposure, duration of treatment and demographic covariates. The change from baseline of the total score on the Symptom Assessment Questionnaire will be the dependent variable of the model.

To: The objectives of pharmacokinetic-pharmacodynamic analysis will be:

1. To assess the relationship between efficacy (as measured by change from baseline of the total symptom score) versus systemic exposure, duration of treatment and covariates.
2. To assess the relationship between the probability to prematurely withdraw from the study versus efficacy, duration of treatment and covariates.

Comment #2 Synopsis, PK/PD # 2

Part 1:Is this indeed an objective? I think that if one calculates the pharmacokinetic parameters, one would calculate the variability from the associated statistical output. It seems redundant.

- *Response: In the pharmacokinetic analysis of sparse data we estimate the parameters and variability of the parameters simultaneously. But inter-subject and intra-subject variability in the parameters and exposures is a question of special interest. This is the reason to include estimation of variability as a separate objective. No changes need to be made.*

Part 2: BTW, no metoclopramide level determination appears to be included in the Schedule of Assessments and Procedures? Am I missing something?

- *Response: There is an item **Scheduled pharmacokinetic samples** in the Schedule of Assessments. Samples are taken on Visits 2, 3, and 4. No changes need to be made.*

Comment # 3 Synopsis, PK/PD #3

Do we have a detailed plan of how we are going to achieve this? I believe that the statistical plan includes analysis of covariates in terms of SAQ scores.

- *Response: See the plan included in the response to comment 1. The statistical plan includes analysis of efficacy for subpopulations, not of pharmacokinetics. No changes need to be made.*

Comment #4 Synopsis – Efficacy (Primary endpoint)

I would prefer to be very specific here in terms of what we define as efficacy. Let's define the primary endpoint as "a change in mean score of at least 3.5 points in the SAQ between the treatment groups and placebo". I think it will help in the review if we are absolutely clear.

- *Response: Section 9.2 fully explains what the primary endpoint is for this protocol. This is the measured value that will be analyzed. Moreover, Section 14.4 also fully explains how it will be analyzed. The value of 3.5 is used solely to determine the minimum difference in means that we want the ability to detect as statistically significant. With regard to the definition of efficacy, the FDA has been very consistent in accepting a statistically significant result ($p < 0.05$) as their definition*

of efficacy. I believe that if we achieve a statistically significant result that the FDA does not deem as clinically significant, then they may not choose to approve the drug. Although we called 3.5 the minimum effect we wish to be able to detect, it does not mean that we are defining efficacy as a difference in means of at least 3.5 points.

Comment #5 Synopsis – Efficacy (Primary endpoint)

What about the secondary endpoints in terms of efficacy? What about the global assessment (and the mechanism for determining it)? What about assessment of trends of individual symptoms (and the definition of the trend?)

- *Response: Section 9.3 fully explains what the secondary endpoints are for this protocol. Section 14.4 also fully explains how these will be analyzed. If Roberts requests, additional information could be added to the synopsis.*

Comment #6 Synopsis Study procedures

We have not defined in the synopsis as to what an "eligible patient is". We need to define it clearly "as a patient diagnosed with diabetes mellitus 1 or 2, at or over the age of 18, (....other) and SAQ score of at least 10 points -out of maximum of 36 points- and a score of 2 points or higher in at least two symptoms -out of nine- included in the SAQ". Also, in study procedures we need to also include the washout period. We may also want to clarify the term "eligible" and "enrollable" because they are not apparently the same. We may want to use the terms "eligible for screening" and "eligible for entry into the study".

- *Response: Synopsis can be modified to incorporate the above comments and information per Roberts request.*

Comment #7 Synopsis, Randomization procedures:

Will this exclude sites unable to enter more than five patients? Is randomization going to be across sites?

- *Response: Section 14.1 notes that all patients with at least one follow-up SAQ will be included in the intent to treat analysis. Randomization will be in blocks of five, and drug will be shipped to sites in blocks of five. Thus, sites that enroll in increments of five will be balanced, and those that don't will not be balanced. The numbers of patients in each treatment group should balance with so many patients.*

Comment # 8 Table of scheduled assessment, footer related to gastric emptying test

I think that we need to define this better.

- *Response: Footnote can be modified to provide an improved definition per Roberts' preference.*

Comment # 9 Figure 1 – Screening box, Page: 7

Why –14 in screening and a 7 day washout?

- *Response: After internal discussion at GloboMax, it is proposed that the screening period be extended up to 28 days. This will ensure adequate time for patients to be screened, randomized and entered into active treatment. Less time would increase the possibility that screening procedures would be outdated prior to entry into treatment. The 7 day washout will be included within this 28 day period. Action: Figure will be modified to be consistent with text of protocol for 28 day screening period if agreed upon.*

Comment #10 Section 6.1 Related to following sentence "All potential study patients will have a baseline evaluation including a medical history, physical examination, assessment of gastric stasis symptoms, laboratory tests, and an assessment of the nasopharynx."

We seem to have changed our tune here. If we are going to do this test on a subset, we need to define the subset and put forth a rationale as to why we think that this subset is appropriate. This is a change not requested by the FDA and upon submission we need to state our reasons for making this change and I think that we need to be very clear on this. We may need to cite as many papers as possible supporting our own assertion that the test is of little diagnostic or predictive value.

- *Response: We would recommend a wording change to the above sentence to change gastric stasis symptoms to "symptom assessment" to clarify this point. The issue of number of sites and subsets of patients with gastric emptying will be addressed in a later response.*

Comment # 11 Section 6.2.1 "Once a patient is deemed eligible to enter into this study.", 1st bullet point

If I remember correctly, we are talking about 14 days in the synopsis, then 14 days and 7 days in the figure. I think we need to be clear.

- *Response: See response to comment #9. Protocol will be reviewed by QA for consistency and accuracy of all number and events.*

Comment # 12 Section 6.2.1 Once a patient is deemed eligible to enter into this study, 2nd bullet point

I think that this is redundant and it can be merged in paragraph 1.

- *Response: We would recommend that both criteria should be included, as the categories are not mutually exclusive; clearly stating both limits any potential for misunderstandings.*

Comment #13 Section 6.2.1 Once a patient is deemed eligible to enter into this study, 3rd bullet point

I will phrase this a bit differently: "For enrollment in the study, eligible patients require an aggregate SAQ score of at least 10 points -out of maximum of 36- , and a score of 2 points or higher in two of the nine symptoms included in the SAQ"

- *Response: The suggested change can be incorporated into the protocol*

Comment #14 Section 6.2.1 Once a patient is deemed eligible to enter into this study, 3rd bullet point related to the following sentence: This is the symptom that the patient reports bothers them the most.

I think that this sentence is redundant but if one needs to include it, it should be simplified

- *Response: We would recommend that the sentence remains but can be modified as needed.*

Comment #15 Section 6.3.
How do we pre-specify these sites?

- *Response: The following wording can be incorporated into the protocol to better define the selection of the sites. "This test will be completed in a subset of patients. This test will only be conducted at a small number of sites, which are capable of performing the gastric emptying test as specified in this protocol. All patients at these pre-specified investigative sites are to be included."*

Comment #16 Section 6.8.1 Rationale for dose selection, last paragraph

This may be the case –and it is not really essential- but the pharmacokinetic studies are not adequate to support dosing for a specific clinical endpoint or indication. One may want to state that the pharmacokinetic data in addition to the existing treatment experience (ref) and/or clinical studies (ref) lead one to propose these two dosing regimens.

- *Response: The protocol can be modified in the following manner:*

From: Based on these results, it was determined appropriate to study both the efficacy and safety of metoclopramide 10 mg and 20 mg for the treatment of diabetic gastroparesis.

To: Based on the existing treatment experience (10 mg of oral metoclopramide), and relative bioavailability of the nasal spray, it was determined appropriate to study safety and efficacy of both 10 and 20 mg doses of nasal spray for the treatment of diabetic gastroparesis

Comment #17 Section 6.8.5 5th Bullet – related to β-agonists

Why?

- *Response: Inhaled β-agonists have very low systemic bioavailability and as such have a predominantly local effect, whereas orally administered β-agonists have a systemic effect-- it is important to limit the exclusions as much as possible to be able to maximize recruitment.*

Comment # 18 Section 7 Last bullet

"Patient lost to follow-up" has a specific meaning that is not applicable here. I think that one would be better to state "Subject withdraws on its own volition". BTW, my suggestion is to apply the term "Subject" rather than "Patient" when we are referring to the study procedures and to patients already enrolled. A patient is not necessarily a "subject".

- *Response: The term follow-up is defined in the protocol. For consistency, the term patient has been used throughout the protocol rather than switching between subject and patient in different sections of the protocol. If Roberts requests, the bullet and subject/patient terminology can be changed as per the recommendation from Ribogene.*

Comment #19 Section 7, 4th of 5 paragraphs, "When a patient is "lost to follow-up"...

I know that it is not dramatic, but the study does not have a treatment and follow-up portion. The treatment is continuous throughout the study, so the term "lost to follow-up" does not apply strictly here. So, we can simplify this by stating that if the "patient fails to attend the evaluation appointment within the appointment window....". BTW, what happens if the subject has interruptions in treatment and/or evaluations? How do we measure compliance? Are we going to measure remaining solution when the drug is returned to the site for a refill?

- *Response: The term follow-up was defined. However to decrease any possibility of confusion the following sentence "When a patient is "lost to follow-up" (fails to return for repeat evaluations), a reasonable effort should be made by the Investigator to contact the patient to determine why he/she failed to return for any necessary follow-up assessments. This information will be documented on the appropriate source documentation and the CRF" can be modified to change the term follow-up to scheduled as shown below:*

When a patient is "lost to follow-up" (fails to return for repeat evaluations), a reasonable effort should be made by the Investigator to contact the patient to determine why he/she failed to return for any necessary scheduled assessments. This information will be documented on the appropriate source documentation and CRF.

With regard to the comment on compliance, weighing or measuring remaining volume would not be practical. We would recommend no change to the protocol at this time.

Comment #20 Section 9.1 1st paragraph

As the Perkel tool is in the literature and it is used for sample size calculation, it may be important to state what the modification were (are there any really apart from language?) and the reasons for these modifications. Again, any departure from precedent should be clearly stated, not only for clarity but for expediting the review.

- *Response: The modifications to the Perkel scale are language changes (medical to layman terminology) and more precise specifications for the scale to increase inter-site consistency. Within this section, a reference is cited for the original Perkel article, and therefore we do not consider additional information is required in this protocol.*

Comment #21 Section 9.2.

Again, we need to clearly define the endpoint for clarity

- *Response: see response to comment # 4*

Comment #22 Section 9.3 Bullet #1

Do we have any specific point differences in mind here? If the Perkel data are available (and I think they are), what was the mean difference there (at least in idiopathic gastroparesis) ?

- *Response: see response to comment #4*

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Comment #23 Section 9.3 Bullet # 3

Although I do not think that this is really a substantial problem, we have already identified the hallmark symptoms of gastroparesis. Are we certain that we want to still include a "cardinal" symptom question and analysis. There is a potential for embarrassment here.

- *Response: The inclusion of a cardinal symptom evaluation was strongly recommended by the Experts. This was reiterated in recent conversations. Cardinal Symptom assessments were also conducted in the Domperidone studies.*

Comment #24 Section 9.3. Bullet #4

Have we decided on this? I thought our decision in the meeting was to write a responders definition!!!

- *Response: During the meeting the decision was that GloboMax would review the global assessment issue and make a recommendation as to whether a 5 point questionnaire or a defined responder assessment should be conducted. Since that time discussions have occurred at Globomax and with the experts, and it is our recommendation that the 5 point questionnaire be used rather that trying to arbitrarily define a responder without scientific rationale for that number.*

Comment #25 Section 9.3 Bullet #5

Why?

- *Response: As per the FDA responses to the protocol the dropouts are now included in the efficacy assessment. Please refer to section 14.4 for further details.*

Comment #26 Section 9.3 Bullet #6

Again, no particular rationale here

- *Response: In response to the FDA comments to the protocol and the minutes from the FDA meeting, it was clear that the FDA does not consider the gastric emptying test to be an indicator of clinical efficacy. Therefore the test is only included in the protocol as an exploratory variable and as such minimal statistical analysis will be performed.*

Comment #27 Section 10.1, 1st paragraph related to AE monitoring. "During the course of the study, the patient will be closely monitored by the study personnel"

How? We have already laid out the visit schedule. Is there going to be an additional monitoring tool?

- *Response: We would recommend that the section be reworded for clarification, however no additional monitoring tool should be considered.*

Comment #28 Section 10.1, 1st paragraph related to AE monitoring. "All AEs will be reported in the CRF and the source documents."

Ineffective, as the patients will be visiting or calling the site weekly. Are they going to keep a journal? Is a weekly interview an effective tool? You suggest otherwise by the "closely monitored" statement. I think that we should be upfront and state exactly what we are going to do. For example, "the subjects will be questioned for adverse experiences during the scheduled evaluation visits and telephone calls".

- *Response: Same as for comment #27.*

Comment #29 Section 10.1.2 last bullet

This definition should be updated to include the latest additions, i.e. investigator's assessment

- *Response: the definition of SAE is consistent with current CFR definitions. No changes are necessary.*

Comment #30 Section 10.1.2 Related to the following statement: "An unexpected event is any AE that is not identified in nature, severity, or frequency in the Reglan® package insert."

Why not include them in the investigators brochure, the usual tool for this assessment? One can state that the use of metoclopramide is known to result occasionally in (list of adverse events).

- *Response: This section can be modified to include reference to the investigator's brochure.*

Comment #31 Section 10.1.2 Related to AE reporting to sponsor.
Reports to the FDA should only be undertaken if the event is unexpected and reasonably associated with the use of the drug. However, the protocol should not necessarily list the obligations of the sponsor but those of the investigator. When should we expect a written report from the site? Is the first report only an oral one?

- *Response: This section of the protocol is consistent with Roberts' standard protocols. If changes are considered necessary Roberts should make that decision.*

Comment #32 Section 10.1.3 Definition of Probably related

Not related is missing

- *Response: Unclear as to the meaning of this comment. The first definition in this section is "Not Related". Need clarification from Ribogene.*

Comment #33 Section 10.2 End of bullet section

What about plasma levels of metoclopramide?

- *Response: Handling of plasma samples is described in Section 12.2*

Comment #34 and #35 Section 10.4
#34 This will result in tremendous number of AEs in this population of patients!!! You may want to enter here a % change (which is what is typically done, such as 20%). Yes, it is arbitrary but what is worsening in an already abnormally elevated measurement (and there will be lots of them)?

#35 You will need to determine the term "significant" here in order to provide guidance to the central lab. Also, why should these be reported to the sponsor? Should they be reported to the clinical or medical monitor for further elucidation?

- *Response: Clinically significant lab values/AEs are determined by the investigator. This is especially important in conducting studies in patient populations where you expect a high number of values "outside the reference range". We cannot assign a predetermined % change to parameters, as this is dependent on the specific test. With regard to the reporting to the sponsor, this is a standard section of the Roberts protocol.*

Comment #36 Section 11, 1st sentence

Have I missed this?

- *Response: See answer to the Comment #2, Part 2*

Comment #37 Section 11, 1st sentence

This is effectively a meta-analysis and it should be treated so and its parameters should be clearly stated. There is a huge debate on meta-analysis and I do not think we want to enter it without some good ground work and clear definitions of the parameters of this analysis. It is all very hazy here.

- *Response: The PK/PD plan is to combine RAW data from two clinical trials identical in design and patient population. The study number will be treated as a covariate and included in the PK model. The issues with mataanalysis regard using the information*

for proof of effectiveness when individual trails fail to have the appropriate level of statistical significance. We are combining data to improve the precision of our estimates, similar to what one does with an Integrated Summary.

Comment #38 Section 12.2

Part 1:OK, this seems to be an add-on without connection with the rest of the study (and it is missing from the overall section of assessments and procedures. Is this a separate blood draw?

- *Response: See response to comment #2 Part 2.*

Part 2: Now that we have beefed up the pharmacokinetic study substantially (doubled the numbers), what is the use of this? It is adding complexity, the metaanalysis can always be a source of trouble, etc, etc.... Is it best to remove this part?

- *Response: See response to the comment # 1 and Comment #37*

Comment #39 Section 14.1 End of 2nd sentence

What is "the baseline symptom assessment questionnaire requirement."? Do you mean patients that should not have been enrolled but were? And we would have missed those throughout the study? Anyway, does the term "per protocol" cover this?

- *Response: The baseline SAQ requirement is a minimum score of 10 and at least a score of 2 on at least two symptoms. Any patient who is enrolled without meeting these criteria will be excluded from the per protocol analysis.*

Comment #40 Section 14.1 End of 2nd paragraph

Why do we have to do this? Can we just mark it as a missing value? Is there a problem in dealing with missing values in our statistical calculations?

- *Response: We are replacing missing values to allow for an analysis of the time course of treatment (i.e. means across the six weeks). This is a commonly used procedure to eliminate the bias due to unequal numbers of patients at each visit.*

Comment #41 Section 14.2

Descriptive statistics will be presented by treatment group for all demographic and baseline variables. Any variable which appears to be imbalanced among the treatment groups will be included as a covariate in a secondary analysis to assess its impact.

- *Response: This says that we will reanalyze the primary endpoint with the effect of the demographic variable included to assess its impact. For example, if the placebo*

group has a substantially greater proportion of males than the other two groups we will then do an analysis which adjusts for sex differences to see if that makes a difference in the results. Would you prefer if we call this an exploratory analysis rather than a secondary analysis?

Comment #42 Section 14.3

We claim that we modified the SAQ (but did not detail the modification) How does the modification affect the score and, therefore, these calculations?

- *Response: We have no data that uses the modified score, hence, our best guess is that the modification has no effect*

Comment #43 Section 14.4 3rd paragraph related to cardinal symptom

I think that we should drop this. Where is the analysis of individual symptoms and the core group of five symptoms?

- *Response: The analysis of individual symptoms is discussed in the second paragraph of Section 14.4. The analysis of the core group of five cardinal symptoms was inadvertently left out of the analysis of secondary endpoints. I will add it.*

Comment #44 Section 14.7

What exactly does this mean? We are not going to calculate frequency of events?

- *Response: This states that if a patient reports a headache on two separate occasions then this patient will only be counted once in the summary of headaches.*